NEW PERSPECTIVES ON HORMONE THERAPY FOR PROSTATE CANCER

Prostate cancer

New perspectives on hormone therapy for prostate cancer

Dr Declan McKenna, Lecturer in the School of Biomedical Sciences at Ulster University, Coleraine, outlines past, present and future perspectives on hormone therapy for prostate cancer

When Dr Charles Huggins took up a new post at the University of Chicago in 1927, he had little interest in cancer biology. A physiologist by training, he was more interested in glandular secretions and was researching how prostatic fluid could control the growth of the prostate. His early animal experiments revealed that if he castrated a dog, its prostate gland would shrink and the prostatic fluid would unsurprisingly dry up.

However, if the castrated dog was then injected with testosterone this response was prevented, demonstrating that the cells of the prostate were dependent on testosterone for growth. But then Huggins started to wonder what would happen if dogs with prostate tumours were deprived of testosterone. Were cancerous prostate cells also dependent on the hormone for growth?

A series of experiments demonstrated that surgical castration of dogs with prostate cancer did indeed slow the tumour growth, and this effect was subsequently shown to work in human patients as well.

It was convincing evidence but Huggins, no doubt aware that removal of their testicles might not be an attractive therapeutic option for most men, took things a step further. Could testosterone action be blocked by adding female hormones to counter the male hormone?

Throughout the 1930s, Huggins embarked on a programme of research that definitively proved that injection of oestrogens could cancel out the effect of testosterone. 'Chemical castration', as he called it, could be used to effectively suppress tumour growth in patients with prostate cancer, with minimal side-effects.

For the first time, someone had proven scientifically that a cancer was dependent on an internal growth signal, a signal that, crucially, could be blocked without resorting to use of a cytotoxic drug. It was a discovery that would pave the way for almost 80 years of research into hormone therapy, which has now become the backbone of prostate cancer treatment.

Pic: Getty Images

Current perspective

Prostate cancer is one of the most common cancers in men, with about one-in-eight men in Ireland estimated to develop the disease at some point in their lives. Surgery, radiotherapy, chemotherapy and androgen deprivation therapy (ADT) are all viable options for initial treatment and five-year survival rates are ~90 per cent overall, illustrating that prostate cancer can often be successfully treated.

Nowadays, ADT encompasses several drugs that can effectively treat prostate cancer (Table 1), while others are in development. For localised, early-stage prostate cancer, ADT generally involves suppressing testosterone production by interfering with the mechanisms that regulate its biosynthesis in the body. Luteinising hormone-releasing hormone (LHRH) agonists stop the pituitary gland producing luteinising hormone (LH), which is needed to stimulate testosterone production in the testes.

However, patients taking LNRH agonists for the first time can experience a phenomenon known as a 'testosterone flare', as excess LH production is briefly stimulated before being blocked.

For this reason, LNRH agonists are often given in combination with an anti-androgen, a drug which competitively blocks testosterone from binding to the androgen receptor (AR), thereby inhibiting AR-dependent growth signalling. Gonadotropin-releasing hormone (GnRH) antagonists also work to inhibit LH action but are less commonly used.

For locally advanced prostate cancer, anti-androgens are generally the favoured option. Importantly, ADT for localised and locally advanced prostate cancer can be used in combination with radiotherapy, as several clinical trials over the past 30 years have shown that this approach can delay tumour progression compared to radiation alone.

However, although patients receiving ADT for early-stage disease initially respond to treatment, they typically relapse within two years to castrate-resistant prostate cancer (CRPC), as mechanisms of androgen independence emerge in the tumour cell population.

Historically, this meant switching treatment to chemotherapy, but in recent years two ADT agents have shown benefit in management of later-stage metastatic CRPC (mCRPC). Enzalutamide is a second-generation anti-androgen, while abiraterone inhibits CYP171A, a key enzyme in the synthesis of testosterone.

Promising results to date and ongoing trials continue to track and compare the benefit of these drugs in advanced prostate cancer. Thus, ADT continues to be the mainstay therapy for management of prostate cancer at its various stages and targeting AR axis signalling remains the focus for development of new ADT drugs.

Nevertheless, the problem of developing drug resistance remains a significant clinical obstacle. Molecular and cellular alterations including gene mutation, AR gene amplification, bypass pathways, ligand-independent activation and growth of cancer stem cells can all contribute to the selection of tumour cells that are no longer dependent on testosterone for growth and which are more likely to develop into incurable mCRPC. The driving forces underlying these changes remain elusive and are the focus of much research.

In our laboratory at Ulster University (UU), we are interested in how tumour hypoxia, a common feature of solid tumours, may exert a selective pressure which encourages the growth of cancer cells with increased metastatic potential.

Using murine xenograft models of prostate cancer, we have shown that the anti-androgen bicalutamide actually induces a profound hypoxia by collapsing the tumour vasculature, resulting in an up-regulation of pro-survival genes by hypoxia-resistant cells within the tumour and increased metastatic potential.

This may help explain why patients relapse after an initially successful response to ADT. It is therefore necessary to consider treatment strategies that can target the resistant cells that escape hormone therapy and this means deciding for any given patient whether administration of ADT should be immediate, deferred, neoadjuvant, adjuvant, intermittent or combined.

This idea of combinatorial drug treatment has gained traction in recent years. In particular, recent results from the CHAARTED and STAMPEDE clinical trials have revealed that use of docetaxel (a taxane drug) in combination with ADT improved relapse-free survival in patients with high-risk localised prostate cancer, proving that combining ADT with other drug types can benefit prostate cancer sufferers.

Other ongoing trials are similarly investigating both the combination and the scheduling of different chemotherapeutic drugs (and/or radiation) with ADT on patient relapse and overall survival. A list of active trials on the island of Ireland can be viewed at the Cancer Trials Ireland (www.cancertrials.ie) and Northern Ireland Cancer Trials Centre (http://www.qub.ac.uk/research-centres/nictc) websites. Meanwhile, pre-clinical research is investigating combination of ADT with new drugs.

At UU, we have recently published work showing that a novel hypoxia-activated prodrug (HAP) improves the ability of bicalutamide to control growth of human prostate tumours in mice. Our data suggest that the HAP becomes activated in the hypoxic conditions induced by bicalutamide treatment and targets the resistant cells that would otherwise survive the hormone treatment.

Our ongoing and future work aims to further demonstrate the potential of HAP usage in combination with other drugs, by measuring the physiological and molecular changes taking place with the tumour in response to treatment.

Future perspective

Although clinical trials to date have undoubtedly provided invaluable data to help improve the effectiveness of ADT, truly tailored therapy will require molecular stratification of patients. Personalised medicine depends on the discovery of molecular biomarkers that can reliably detect disease and track response to treatment.

Hence, there is a need for future studies that incorporate longitudinal genomic profiling to help assess which combinations and scheduling of therapies can overcome ADT resistance.

Advances in genomic technology and increased use of next-generation technologies means that vast arrays of data detailing the genetic complexities and characteristics of individual prostate tumours have been gathered. Comprehensive bioinformatics analyses of this data reveal a wide heterogeneity and molecular diversity in prostate tumours, which helps explain why patients presenting with pathologically similar tumours can have very different responses to the same treatment.

The key to improved patient stratification in the clinic therefore lies in both understanding the different sub-types of prostate cancer that exist and determining which treatments these sub-types will best respond to. For example, primary prostate cancers exhibit a wide variability in AR activity, with increased AR-dependent signalling linked to gene mutations in SPOP and FOXA1.

Knowing whether a tumour carries these mutations or not can help determine the most appropriate ADT approach for a patient, and subsequent tracking of their mutational status can inform adaptive drug administration. Likewise, knowing the mutational status of AR itself will be critical in helping predict treatment outcome.

For instance, enzalutamide cannot bind to an abnormal version of the AR called AR-V7, so patients harbouring this mutation would be unlikely to respond to that particular drug, further emphasising the need to stratify patients by molecular profiles. Indeed, recent research has shown that AR-V7 can be detected in patient blood samples and efforts to validate this screening for clinical application are under way.

Similarly, in our lab, we are excited about the potential of microRNAs as markers of disease and treatment response. These small RNA molecules are much more stably preserved than mRNA in clinical samples and can be readily detected in tissue, serum and urine specimens, making them very attractive candidates for non-invasive biomarkers of prostate cancer.

Developing precision medicine for individual patients is no small undertaking, but it is not an impossible goal. Clinicians, researchers, industry and health professionals across the world are continually developing innovative approaches for the detection and treatment of prostate cancer, while patients themselves are ever more informed about participation in clinical trials and their own treatment plans.

Treatment of prostate cancer has made huge strides since Charles Huggins' breakthrough work, but his words are still as relevant as ever. "Discovery is our business," he once told his colleagues. "Make damn good discoveries." As a research community, we are aiming to make discoveries so good, they will mean no man need die of prostate cancer.

References on request.

Table 1: Selection of ADT drugs currently used for treatment of prostate cancer

Type	Drug Name	Brand Name
LHRH agonists	goserelin	Zoladex®, Novgos®
	leuprorelin acetate	Prostap®
	buserelin acetate	Suprefact®
	triptorelin	Decapeptyl®, Gonapeptyl Depot®
	histrelin	Vantas®
GnRH antagonist	degarelix	Firmagon®
Anti-androgens	bicalutamide	Casodex®
	flutamide	Drogenil®
	cyproterone acetate	Cyprostat®
	enzalutamide	Xtandi®
CYP171A inhibitor	abiraterone	Zytiga®
Oestrogen	diethylstilbestrol	Stilboestrol®

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